(FILE 'MEDLINE, CANCERLIT, EMBASE, BIOSIS, BIOTECHDS, CAPLUS' ENTERED AT 17:03:04 ON 21 JAN 2004)

DEL HIS

L1 20 S GGGG? AND CPG

L2 7 DUP REM L1 (13 DUPLICATES REMOVED)

L9 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:464425 CAPLUS
DN 119:64425
TI Nucleotide sequence of a representative member of a Trypanosoma cruzi dispersed gene family
AU Wincker, Patrick; Murto-Dovales, Ana Cristina; Goldenberg, Samuel
CS Dep. Bioquim. Biol. Mol., Fund. Oswaldo Cruz, Rio de Janeiro, 21040, Brazil
SO Molecular and Biochemical Parasitology (1992), 55(1-2), 217-20
CODEN: MBIPDP; ISSN: 0166-6851
DT Journal
LA English
AB The authors previously reported the isolation and restriction mapping of three .lambda. EMBL4 genomic clones from T. cruzi clone Dm 28c that contain all or part of one copy of the gene family DGF-1. The sequenced region comprises most of the restriction fragments of the DGF-1 gene, which are known to be repeated in the T. cruzi genome [1]. It encompasses 11,154 bp. The authors consider the sequenced region presented here as the central portion of DGF-1. A large coding region is seen in only one of the six possible frames. It encompasses 9687 nucleotides starting from the first ATG at position 1043 and ending with TGA at 10729. The codon usage is similar to that of other sequenced genes of T. cruzi. The DNA sequence upstream from the first ATG and downstream from the first TGA of the ORF contains multiple stop codons in all three reading frames. This indicates that the ORF characteristic of the DGF-1 family may not extend far beyond these endpoints, even if the latter arise as mutations peculiar to DGF-1.1. Starting from the first inframe methionine residue, the authors predict a product of 3229 amino acids with a mol. wt. of 335,000. It is rich in **hydrophobic** amino acids, **serine** and threonine. It displays 31 potential N-glycosylation sites and a 73-amino-acid region with many potential O-glycosylation sites. The first two start codons (positions 1 and 77) are followed by sequences characteristic of signal peptides. The main feature of the sequence is the presence of a repeated motif contg. 8 cysteine residues at conserved positions. They delineate a 63-74-aa region repeated 7 times in the polypeptide chain. Few amino acids are conserved in this motif except for the 8 cysteines. The **spacer** sequence between each motif is very poorly conserved, but its size is quite const., ranging from 307 to 355 aa. Various families of eukaryotic cell-surface receptors are known to share conserved Cys-rich repeats of different sequence classes in their extracellular domain. It is generally believed that each external Cys-rich sequence type defines the basis of a specific protein-protein interaction. The motif in DGF-1 has not been found in data base searches, and may therefore belong to an as yet undescribed receptor class. A region rich in proline appears uniquely between the 4th and 5th Cys-rich repeats. Addnl., the presence of two Arg-Gly-Asp tripeptides at positions 272-274 and 777-779 was obsd. Arg-Gly-Asp-mediated interaction of T. cruzi with host cells has been previously documented. The presence of four **hydrophobic** stretches at the carboxy terminus of the mols. is noted. One or more of them may serve as a membrane anchor.

L2 ANSWER 4 OF 7 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 1996-05191 BIOTECHDS
TI New immunomodulatory oligonucleotides; containing an unmethylated **CpG** dinucleotide for stimulating activity or methylated for inhibitory activity; application in immune deficiency disease therapy and diagnosis
AU Krieg A M
PA Univ.Iowa-Res.Found.
LO Iowa City, IA, USA.
PI WO 9602555 1 Feb 1996
AI WO 1995-US1570 7 Feb 1995
PRAI US 1994-276358 15 Jul 1994
DT Patent
LA English
OS WPI: 1996-105847 [11]
AB An oligonucleotide (ON) is claimed, comprising 2-100 nucleotides and containing at least 1 unmethylated **CpG** dinucleotide. Also claimed are: i. a method for treating a disease associated with an immune system activation which comprises administering a neutral ON alone or in conjunction with a carrier; ii. an improved method for performing antisense therapy comprising methylating **CpG**-containing ONs prior to administration; iii. an improved method for in vivo diagnosis using ON probes comprising methylating **CpG**-containing ONs prior to administration; iv. an ON which is capable of interfering with the activity of viral or cellular transcription factors and containing a consensus immunoinhibitory **CpG** motif of formula (I) 5'-GCGXnGCG-3', where X = nucleotide, and n = 0-50. 2 Specific ONs are claimed: 5'-**GGGGTCAACGTTGAGGGGGG**-3' and (I) where Xn is a **CpG** dinucleotide. The unmethylated **CpG**-containing ONs can be used to activate B-lymphocytes and natural killer cells (claimed). They can be used for treating, preventing or ameliorating an immune system deficiency (claimed), e.g. a tumor or cancer or a viral, fungal, bacterial or parasitic infection in a subject. (45pp)

L2 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1
AN 2001285392 MEDLINE
DN 21116983 PubMed ID: 11179339
TI Interleukin-12- and gamma interferon-dependent protection against malaria conferred by **CpG** oligodeoxynucleotide in mice.
CM Erratum in: Infect Immun 2002 Sep;70(9):5338
AU Gramzinski R A; Doolan D L; Sedegah M; Davis H L; Krieg A M; Hoffman S L
CS Malaria Program, Naval Medical Research Center, Silver Spring, Maryland 20910-7500, USA.
SO INFECTION AND IMMUNITY, (2001 Mar) 69 (3) 1643-9.
Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010529
Last Updated on STN: 20020921
Entered Medline: 20010524
AB Unmethylated **CpG** dinucleotides in bacterial DNA or synthetic oligodeoxynucleotides (ODNs) cause B-cell proliferation and immunoglobulin secretion, monocyte cytokine secretion, and activation of natural killer (NK) cell lytic activity and gamma interferon (IFN-gamma) secretion in vivo and in vitro. The potent Th1-like immune activation by **CpG** ODNs suggests a possible utility for enhancing innate immunity against infectious pathogens. We therefore investigated whether the innate immune response could protect against malaria. Treatment of mice with **CpG** ODN 1826 (TCCATGACGTTCCTGACGTT, with the **CpG** dinucleotides underlined) or 1585 (**ggGGTCAACGTTGAggggggG**, with g representing diester linkages and phosphorothioate linkages being to the right of lowercase letters) in the absence of antigen 1 to 2 days prior to challenge with Plasmodium yoelii sporozoites conferred sterile protection against infection. A higher level of protection was consistently induced by **CpG** ODN 1826 compared with **CpG** ODN 1585. The protective effects of both **CpG** ODNs were dependent on interleukin-12, as well as IFN-gamma. Moreover, CD8+ T cells (but not CD4+ T cells), NK cells, and nitric oxide were implicated in the **CpG** ODN 1585-induced protection. These data establish that the protective mechanism induced by administration of **CpG** ODN 1585 in the absence of parasite antigen is similar in nature to the mechanism induced by immunization with radiation-attenuated P. yoelii sporozoites or with plasmid DNA encoding preerythrocytic-stage P. yoelii antigens. We were unable to confirm whether CD8+ T cells, NK cells, or nitric oxide were required for the **CpG** ODN 1826-induced protection, but this may reflect differences in the potency of the ODNs rather than a real difference in the mechanism of action of the two ODNs. This is the first report that stimulation of the innate immune system by **CpG** immunostimulatory motifs can confer sterile protection against malaria.

L2 ANSWER 1 OF 7 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2003-19559 BIOTECHDS
TI Treating cancer, involves administering tumor-derived dendritic cell inhibitory factor antagonist in combination with Toll-like receptor agonist, to an individual in need of the treatment;
recombinant antagonist and agonist for administration in cancer mouse animal model for cancer therapy
AU VICARI A P; CAUX C
PA SCHERING CORP
PI WO 2003045431 5 Jun 2003
AI WO 2002-US38098 26 Nov 2002
PRAI US 2001-333434 27 Nov 2001; US 2001-333434 27 Nov 2001
DT Patent
LA English
OS WPI: 2003-493377 [46]
AB DERWENT ABSTRACT:
NOVELTY - Treating cancer, involves administering an effective amount of a tumor-derived dendritic cell (DC) inhibitory factor antagonist (I) in combination with an effective amount of Toll-like receptor (TLR) agonist (II), to an individual in need of the treatment.

BIOTECHNOLOGY - Preferred Method: (I) is selected from antagonists of interleukin (IL)-6, vascular endothelial growth factor (VEGF), cytotoxic T lymphocyte antigen, Cytotoxic T-lymphocyte associated molecule-4 (CTLA-4), OX-40, transforming growth factor (TGF)-B, prostaglandin, ganglioside, macrophage-colony stimulating factor (M-CSF) and IL-10 or IL-10 receptor. IL-10 antagonist is recombinant, a natural ligand, small molecule, an antibody or its fragment, antisense nucleotide sequence or a soluble IL-10 receptor molecule. (II) is recombinant, a natural ligand, immunostimulatory nucleotide sequence, small molecule, purified bacterial extract or an inactivated bacterial preparation. (II) is TLR-9 or an immunostimulatory nucleotide sequence e.g. **CpG** motif selected from **CpG** 2006 (TCGTCGTTTGTCGTTTTGTCGTT), **CpG** 2216 (**GGGGGACGATCGTCGGGGGG**), AAC-30 (ACCGATAACGTTGCCGGTGACGGCACCACG) and GAC-30 (ACCGATGACGTCGCCGGTGACGGCACCACG). The immunostimulatory nucleotide molecule is stabilized by structure modification such as phosphorothioate-modification, or is encapsulated in cationic liposomes. The method further involves administering a substance which allows for slow release of (I) and (II) at a delivery site, and at least one tumor-associated antigen linked to TLR agonist. The tumor-associated antigen is selected from any one of the compounds given in the specification, e.g. Melan-A, tyrosinase, p97 and high molecular weight melanoma antigen. The method further involves administering an activating agent e.g. interferon (IFN)-alpha, TNFalpha, RANK ligand/agonist, CD40 ligand/agonist, or a ligand/agonist of another member of the TNF/CD40 receptor family. The method further involves delivering a chemokine (e.g. CCL21, CCL3, CCL20, CCL16, CCL5, CCL25, CXCL12, CCL17, CCL8, CCL2, CCL13, CXCL9, CXCL10 and CXCL11) active on dendritic cells, to the tumor. The chemokine is delivered to the tumor using a targeting construct comprising a chemokine or a biologically active fragment or its variant, and a targeting moiety. The targeting moiety is selected from a peptide of at least 10 amino acids, a protein, a small molecule, a vector or an antibody or its fragment. (I) and (II) are linked to each other, and further linked to a tumor associated antigen.

ACTIVITY - Cytostatic. C26-6CK tumor cells (1x105 cells) were implanted subcutaneously at Day 0 in groups of seven 8-week old female BALB/c mice. Ten mug of **CpG** 1668 was injected peri- (when tumor too small) or intratumorally at Day 7,14 and 21. Anti-IL-10R purified antibody (250 mug) was injected intraperitoneally twice a week starting at Day 7 (stop Day 24). Control antibody was purified GL113 antibody. Tumor development was assessed three times a week by palpation and tumors measured using calipers with tumor volume = I2xLx0.4, where I is the small diameter and L is the large diameter. Mice were sacrificed when

tumors exceeded 1500 mm3 or more for human criteria. The results showed that all the mice injected with control antibody or anti-IL-10R antibody alone developed tumors within 7-10 days, that eventually led to the sacrifice of animals at around 4 weeks. Injection of the TLR-9 agonist **CpG** 1668 had a minor effect since 1/7 mouse did not develop a tumor. In addition, survival was slightly better than this **CpG** 1668 group and the mean volume of tumors smaller than in the control group after 3 weeks. In contrast, mice treated with the combination of **CpG** 1668 and anti-IL-10R, although developing palpable tumors, rejected these tumors for 6 out of 7 mice. Subsequently, those mice remained tumor-free for the rest of the experiment. The results indicated that the combination of TLR-9 agonist and IL-10 antagonist has therapeutic value in the C26-6CK model, suggesting that it could be used to treat other tumors, including in man.

MECHANISM OF ACTION - Activator of dendritic cells that are rendered hypo-responsive to activation stimuli by the disease.

USE - The method is useful for treating cancer e.g. melanoma, breast, pancreas, colon, lung, glioma, hepatocellular, endometrium, gastric, intestinal, renal, prostate, thyroid, ovarian, testicular, liver, head and neck, colorectal, esophagus, stomach, eye, bladder, glioblastoma and metastatic carcinomas (claimed).

ADMINISTRATION - (I) and (II) are administered through intravenous, intratumoral, intradermal, intramuscular, subcutaneous or topical route (claimed). Dosage of (I) is 0.05-25 microg/kg/day, preferably 1-10 microg/kg/day, and dosage of (II) is 0.1-100 microg. (47 pages)

L2 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1

Freeform Search

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Term: poly G with CpG

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DATE: Wednesday, January 21, 2004 Printable Copy Create Case

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L4	poly G with CpG	26	L4
L3	poly G with CpG	26	L3
L2	GGGG motif and CpG	2	L2
L1	CpG motif with GGGG$	7	L1

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L3: Entry 2 of 26 File: PGPB Oct 9, 2003

DOCUMENT-IDENTIFIER: US 20030191079 A1
TITLE: Methods for treating and preventing infectious disease

Detail Description Paragraph:
[0083] Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g., Table 1, ODN 4e). Among the forty-eight 8 base ODN tested, a highly stimulatory sequence was identified as TCAACGTT (SEQ. ID. NO: 90) (ODN4) which contains the self complementary "palindrome" AACGTT (SEQ. ID. NO: 105). In further optimizing this motif, it was found that ODN containing Gs at both ends showed increased stimulation, particularly if the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages. ODN 1585 (5' GGGGTCAACGTTGACGGGGG3' (SEQ ID NO: 12)), in which the first two and last five internucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation included by ODN 1638, which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. The effect of the G-rich ends is cis; addition of an ODN with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation. For nucleic acid molecules longer than 8 base pairs, non-palindromic motifs containing an unmethylated CpG were found to be more immunostimulatory.

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L3: Entry 3 of 26 File: PGPB Jul 24, 2003

DOCUMENT-IDENTIFIER: US 20030139364 A1
TITLE: Methods and products for enhancing immune responses using imidazoquinoline compounds

Summary of Invention Paragraph:
[0015] In still other embodiments, the method further comprises administering an immunostimulatory nucleic acid to the subject. In certain embodiments, the agent is administered prior to the immunostimulatory nucleic acid. The immunostimulatory nucleic acid may be selected from the group consisting of a CpG nucleic acid and a poly-G nucleic acid. In certain embodiments, the immunostimulatory nucleic acid is selected from the group consisting of a poly-T nucleic acid, a T-rich nucleic acid, a TG nucleic acid, a CpI nucleic acid and a methylated CpG nucleic acid. In some embodiments, the immunostimulatory nucleic acid has a backbone modification. The backbone modification may be selected from the group consisting of a phosphorothioate modification and a peptide modification (such as for example a morpholino backbone modification), but is not so limited. In one embodiment, the immunostimulatory nucleic acid has a backbone that is chimeric. In still another embodiment, the immunostimulatory nucleic acid is a nucleic acid that is free of CpG, T-rich or poly-G motifs. In some embodiments, the immunostimulatory nucleic acid with a phosphorothioate modified backbone is free of a CpG motif, a T-rich motif or a poly-G motif. The immunostimulatory nucleic acid may be a nucleic acid which stimulates a Th1 immune response. In some embodiments, the immunostimulatory nucleic acid which stimulates a Th1 immune response is not a CpG nucleic acid. In other embodiments, the immunostimulatory nucleic acid which stimulates a Th1 immune response is not a T-rich nucleic acid.

Detail Description Paragraph:
[0135] Immunostimulatory nucleic acids may possess immunostimulatory motifs such as CpG, poly-G, poly-T, TG, methylated CpG, CpI, and T-rich motifs. In some embodiments of the invention, any nucleic acid, regardless of whether it possesses an identifiable motif, can be used in the combination therapy to modulate an immune response. Immunostimulatory backbones include, but are not limited to, phosphate modified backbones, such as phosphorothioate backbones. Immunostimulatory nucleic acids have been described extensively in the prior art and a brief summary of these nucleic acids is presented below.

Detail Description Paragraph:
[0145] Another important subset of non-CpG immunostimulatory nucleic acids are poly-G immunostimulatory nucleic acids. A variety of references, including Pisetsky and Reich, 1993 Mol. Biol. Reports, 18:217-221; Krieger and Herz, 1994, Ann. Rev. Biochem., 63:601-637; Macaya et al., 1993, PNAS, 90:3745-3749; Wyatt et al., 1994, PNAS, 91:1356-1360; Rando and Hogan, 1998, In Applied Antisense Oligonucleotide Technology, ed. Krieg and Stein, p. 335-352; and Kimura et al., 1994, J. Biochem. 116, 991-994 also describe the immunostimulatory properties of poly-G nucleic acids. In accordance with the invention, poly-G-containing nucleotides are useful for treating and preventing bacterial, viral and fungal infections, and can thereby be used to minimize the impact of these infections on the treatment of cancer patients.

Detail Description Paragraph:

[0148] The immunostimulatory nucleic acids of the invention can also be those which do not possess CpG, poly-G, or T-rich motifs.

CLAIMS:

6. The method of claim 5, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid and a poly-G nucleic acid.

22. The method of claim 16, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid and a poly-G nucleic acid.

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L3: Entry 7 of 26 File: PGPB Mar 27, 2003

DOCUMENT-IDENTIFIER: US 20030060440 A1
TITLE: Oligodeoxynucleotide and its use to induce an immune response

Detail Description Paragraph:
[0211] The intracellular localization of these two types of ODN was examined by confocal microscopy of labeled monocytes. K and D ODN largely occupied discrete areas within the same cell, although there was a limited degree of co-localization. D ODN largely occupied punctuated vesicles, whereas K ODN were more diffusely distributed, staining the nucleus as well as cytoplasmic vesicles. This difference in localization was associated with the presence or absence of a poly G tail, since control (non-CpG) ODN with a poly G tail showed the same distribution pattern as did D ODN. In contrast, the fluorescent dyes used did not influence distribution, since switching dyes had no effect on ODN localization pattern.

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L3: Entry 10 of 26 File: PGPB Mar 13, 2003

DOCUMENT-IDENTIFIER: US 20030050263 A1
TITLE: Methods and products for treating HIV infection

Summary of Invention Paragraph:
[0085] Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g. ODN 4e). Among the forty-eight 8 base ODN tested, the most stimulatory sequence identified was TCAACGTT (ODN 4) which contains the self complementary "palindrome" AACGTT. In further optimizing this motif, it was found that ODN containing Gs at both ends showed increased stimulation, particularly if the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages. ODN 1585 (5' GGGGTCAACGTTCAGGGGGG 3' (SEQ ID NO: 1)), in which the first two and last five internucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation induced by ODN 1638, which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. The effect of the G-rich ends is cis; addition of an ODN with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation.

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L3: Entry 11 of 26 File: PGPB Mar 13, 2003

DOCUMENT-IDENTIFIER: US 20030050261 A1
TITLE: Immunostimulatory nucleic acid molecules

Detail Description Paragraph:
[0075] Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g. Table 1, ODN 4e). Among the forty-eight 8 base ODN tested, the most stimulatory sequence identified was TCAACGTT (ODN 4) which contains the self complementary "palindrome" AACGTT. In further optimizing this motif, it was found that ODN containing Gs at both ends showed increased stimulation, particularly if the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages. ODN 1585 (5' GGGGTCAACGTTGAGGGGGG 3' (SEQ ID NO:12)), in which the first two and last five internucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation induced by ODN 1638, which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. The effect of the G-rich ends is cis; addition of an ODN with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation. For nucleic acid molecules longer than 8 base pairs, non-palindromic motifs containing an unmethylated CpG were found to be more immunostimulatory.

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L3: Entry 13 of 26 File: PGPB Feb 6, 2003

DOCUMENT-IDENTIFIER: US 20030026782 A1
TITLE: IMMUNOMODULATORY OLIGONUCLEOTIDES

Summary of Invention Paragraph:
[0052] Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g. ODN 4e). Among the forty-eight 8 base ODN tested, the most stimulatory sequence identified was TCAACGTT (ODN 4) which contains the self complementary "palindrome" AACGTT. In further optimizing this motif, it was found that ODN containing Gs at both ends showed increased stimulation, particularly if the the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages. ODN 1585 (5' GGGGTCAACGTTCAGOGGGG 3' (SEQ ID NO:1)), in which the first two and last five internucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation induced by ODN 1638, which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. The effect of the G-rich ends is cis; addition of an ODN with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation.

L4: Entry 19 of 26 File: USPT Nov 25, 2003

DOCUMENT-IDENTIFIER: US 6653292 B1
TITLE: Method of treating cancer using immunostimulatory oligonucleotides

Detailed Description Text (39):
Of those tested, ODNs shorter than 8 bases were non-stimulatory (e.g., Table 1, ODN 4e). Among the forty-eight 8 base ODN tested, a highly stimulatory sequence was identified as TCAACGTT (SEQ. ID. NO: 90) (ODN4) which contains the self complementary "palindrome" AACGTT (SEQ. ID. NO: 105). In further optimizing this motif, it was found that ODN containing Gs at both ends showed increased stimulation, particularly if the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages. ODN 1585 (5'GGGGTCAACGTTGAGGGGGG 3' (SEQ ID NO:12)), in which the first two and last five internucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation included by ODN 1638, which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. The effect of the G-rich ends is cis; addition of an ODN with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation. For nucleic acid molecules longer than 8 base pairs, non-palindromic motifs containing an unmethylated CpG were found to be more immunostimulatory.

L4: Entry 20 of 26 File: USPT Aug 6, 2002

DOCUMENT-IDENTIFIER: US 6429199 B1
TITLE: Immunostimulatory nucleic acid molecules for activating dendritic cells

Detailed Description Text (58):
Of those tested, oligodeoxyribonucleotides shorter than 8 bases were non-stimulatory (e.g. Table 1, ODN 4e). Among the forty-eight 8 base oligodeoxyribonucleotide tested, a highly stimulatory sequence was identified as TCAACGTT (ODN 4) which contains the self complementary "palindrome" AACGTT. In further optimizing this motif, it was found that oligodeoxyribonucleotide containing Gs at both ends showed increased stimulation, particularly if the oligodeoxyribonucleotide were rendered nuclease resistant by phosphorothioate modification of the terminal intemucleotide linkages. Oligodeoxyribonucleotide 1585 (5' GGGGTCAACGTTCAGGGGGG 3') (SEQ ID NO: 47), in which the first two and last five intemucleotide linkages are phosphorothioate modified caused an average 25.4 fold increase in mouse spleen cell proliferation compared to an average 3.2 fold increase in proliferation induced by oligodeoxyribonucleotide 1638 (5' AAAATCAACGTTGAAAAAAA 3'), which has the same sequence as ODN 1585 except that the 10 Gs at the two ends are replaced by 10 As. Th effect of the G-rich ends is cis; addition of an oligodeoxyribonucleotide with poly G ends but no CpG motif to cells along with 1638 gave no increased proliferation. For nucleic acid molecules longer than 8 base pairs, non-palindromic motifs containing an unmethylated CpG were found to be more immunostimulatory.

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L4: Entry 25 of 26 File: DWPI Nov 7, 2002

DERWENT-ACC-NO: 2003-166150
DERWENT-WEEK: 200316

TITLE: Pharmaceutical composition for treatment of anemia, thrombocytopenia and neutropenia comprises an immunostimulatory nucleic acid and a medicament for the respective disease

Basic Abstract Text (4):
(2) treating or preventing anemia, thrombocytopenia or neutropenia involving administering (A) selected from a methylated CpG nucleic acid, a T-rich nucleic acid, a poly-G nucleic acid and/or a nucleic acid having a phosphorothioate backbone. (A) Having a phosphorothioate backbone is not a CpG nucleic acid; and